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# Persistent Environmental Pollutants and Couple Fecundity: The LIFE Study

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**List of abbreviations:**

CI, confidence interval

DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene

DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane

EDC, endocrine disrupting chemical

Et-PFOSA-AcOH, 2-(N-ethyl-perfluorooctane sulfonamido) acetate

FOR, fecundability odds ratio

hCG, human chorionic gonadotrophin

LIFE, Longitudinal Investigation of Fertility and the Environment

LOD, limit of detection

Me-PFOSA-AcOH, 2-(N-methyl-perfluorooctane sulfonamido) acetate

OCPs, organochlorine pesticides

PBB, polybrominated biphenyl

PBDEs, polybrominated diphenyl ethers

PCB, polychlorinated biphenyls

PFC, perfluorochemicals

PFDeA perfluorodecanoate

PFNA, perfluorononanoate

PFOSA, perfluorooctane sulfonamide

PFOS, perfluorooctane sulfonate

PFOA, perfluorooctanoate

TTP, time-to-pregnancy

**Abstract**

Background: Evidence suggesting that persistent environmental pollutants may be reproductive toxicants underscores the need for prospective studies of couples for whom exposures are measured.

Objectives: To determine the relation between selected persistent pollutants and couple fecundity as measured by time-to-pregnancy.

Methods: A cohort comprising 501 couples discontinuing contraception to become pregnant was prospectively followed for 12 months of trying to conceive or until a human chorionic gonadotrophin test confirmed pregnancy. Couples completed daily journals on lifestyle and provided biospecimens for the quantification of 9 organochlorine pesticides, 1 polybrominated biphenyl, 10 polybrominated diphenyl ethers, 36 polychlorinated biphenyls (PCBs), and 7 perfluorochemicals (PFCs) in serum. Using Cox models for discrete time, fecundability odds ratios (FORs) and 95% confidence intervals (CIs) were estimated separately for each partner's concentrations adjusting for age, body mass index, serum cotinine, serum lipids (except for PFCs), and study site (Michigan or Texas); sensitivity models further adjusted for left truncation or time off contraception (≤2 months) before enrollment.

Results: The adjusted reduction in fecundability associated with standard deviation increases in log-transformed serum concentrations ranged between 18%-21% for PCB congeners 118, 167, 209, and perfluorooctane sulfonamide in females, and 17%-29% for *p,p'*-DDE and PCB congeners 138, 156, 157, 167, 170, 172, and 209 in males. The strongest associations were observed for PCB 167 (FOR 0.79; 95% CI 0.64, 0.97) in females and PCB 138 (FOR=0.71; 95% CI 0.52, 0.98) in males.

Conclusions: In a couple-based prospective cohort study with preconception enrollment and quantification of exposures in both female and male partners, a subset of persistent environmental chemicals were associated with reduced fecundity.

## Introduction

The impact of persistent environmental chemicals on human reproduction is a topic of considerable interest. While a number of persistent environmental chemicals or their metabolites have been detected in semen, follicular fluid, and genital tract fluid (DeFelip et al. 2004; Jirsová et al. 2010; Wagner et al. 1990), questions remain about their bioavailability and ability to impact the series of highly interrelated and timed processes underlying successful human reproduction. Experimental and human evidence suggests that persistent environmental contaminants may be associated with reduced follicle count, altered estrous or menstrual cycles, ovulation inhibition, as well as increased pregnancy loss and resorption in humans and animals, respectively (Buck Louis et al. 2011a; Lione 1988; Nicolopoulou-Stamati and Pitsos 2001; Pocar et al., 2003; Torf et al. 2004).

To our knowledge, only one previous cohort study measured serum POPs in women who were recruited prior to conception and followed through 12 observed menstrual cycles (Buck Louis et al. 2009). However, there is evidence suggesting a reduction in female fecundity, as measured by a longer time-to-pregnancy (TTP), associated with persistent environmental chemicals such as 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), dioxin, perfluorochemicals (PFCs), polybrominated diphenyl ethers (PBDEs), and PCBs (Axmon et al. 2005; Eskenazi et al. 2010; Fei et al. 2009; Gesink Law et al. 2005, Harley et al. 2010, respectively) when measured in female partners. In general, previous studies have quantified exposures in women at varying times during pregnancy, instead of measuring exposures during the critical preconception window (Bloom et al. 2009). Studies of pregnant women systematically exclude women who are unable to become pregnant, who may be the most

heavily exposed. In addition, studies of pregnant women rely upon retrospectively reported TTP, which has been shown to result in both under- and over-reporting of TTP (Cooney et al., 2009).

Against a background of speculation that human fecundity may be declining (Lutz et al. 2003; Skakkebaek et al. 2001), possibly due to effects of environmental factors on both partners of the couple as well as lifestyle changes, we designed the Longitudinal Investigation of Fertility and the Environment (LIFE) Study of persistent environmental chemicals and couple fecundity. By design, we sought to explore a spectrum of persistent environmental chemicals measured in both partners in relation to couple fecundability, consistent with the couple dependent nature of human reproduction (Buck Louis 2011a).

**Methods**

*Study design and cohort*. The LIFE Study utilized a prospective cohort design with preconception recruitment of couples that were discontinuing contraception for the purpose of becoming pregnant. The cohort, sampled from an enumerated target population, comprised couples of reproductive age who resided in specific geographic counties in Michigan or Texas with reported environmental exposure to persistent environmental chemicals, and who were planning pregnancy in the next six months. Given the absence of established sampling frameworks for recruiting couples planning pregnancy, we utilized a commercially available marketing database and a fishing/hunting license registry to recruit 501 couples between 2005-2007 from the counties in the two states. Inclusion criteria were age 18-40 years for females and age ≥18 years for males; in a committed relationship; neither partner medically/surgically sterile; female's menstrual cycle between 21-42 days; no injectable contraceptives within 12 months; off

contraception for <2 months; and an ability to communicate in English or Spanish. Introductory letters were mailed to the targeted cohort (n=424,423) followed by telephone screening to identify eligible couples (n=1,184) from which 501 (42%) couples were enrolled (Buck Louis et al. 2011b).

*Data and biospecimen collection*. All data collection occurred in the couples' home. At the start of the study visit, the female partner provided a urine sample that was tested with a home pregnancy test capable of detecting 25 mIU/mL of human chorionic gonadotropin (hCG) to ensure she was not pregnant. This important step permitted us to differentiate between couples achieving pregnancy in the first few weeks following enrollment (i.e., with no menstrual cycle occurring between enrollment and pregnancy) versus during the first fully observed cycle, which we denote in the analysis as cycles 0 and 1, respectively. Each partner of the couple was interviewed separately by one of two research assistants. Interviews were followed by a standardized physical anthropometric assessment (Lohman et al. 1988) to determine body mass index, and the collection of blood and urine samples. Specifically, ≈20cc of nonfasting blood and ≈120cc of urine were collected from each partner of the couple. Blood collection equipment was determined to be free of the contaminants under study. Couples were instructed in the completion of daily journals regarding sexual intercourse and lifestyle factors (e.g., cigarette smoking); female journals also recorded menstruation and home pregnancy test results. Couples had the option of completing journals either in hardcopy or online.

Female partners were instructed in the use of the Clearblue® Easy home fertility monitor (Swiss Precision Diagnostics formerly Unipath). This urinary based monitor tracks the rise in estrone-3-glucuronide ($E_3G$) and luteinizing hormone (LH) across the follicular phase of the

ovarian cycle, and displays a prompt that ranges from low to peak fertility to help the couple time intercourse relative to ovulation. We utilized the monitor to enhance couples' ability to conceive, given that it is 99% accurate in detecting the LH surge compared to the gold standard of vaginal ultrasonology (Behre et al. 2000). The monitor also was intended to minimize cycles that were not at risk for pregnancy (i.e., without sexual intercourse during the peri-ovulation window) which might erroneously lengthen TTP. Women also were trained in the use and interpretation of the Clearblue® Easy home pregnancy test, which is a digital device that indicates the test result as either pregnant or not pregnant. All participants were remunerated $75 for full participation in the study. Human subjects' approval was received from all collaborating institutions. All participants gave informed consent before participation.

*Toxicologic analysis*. All analyses were conducted by the Division of Laboratory Sciences in the National Center for Environmental Health at the Centers for Disease Control and Prevention using established protocols for the quantification of persistent environmental chemicals in serum including: 1) one polybrominated biphenyl (PBB 153); 2) nine organochlorine pesticides (OCPs) (i.e., hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), gamma-hexachlorocyclohexane (γ-HCH), oxychlordane, trans-nonachlor, *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, and mirex); 3) ten PBDEs (congeners 17, 28, 47, 66, 85, 99, 100, 153, 154, 183); 4) thirty-six PCBs (congeners 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, 209); and 4) seven PFCs (2-(N-ethyl-perfluorooctane sulfonamido) acetate (Et-PFOSA-AcOH), 2-(N-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), perfluorodecanoate

(PFDeA), perfluorononanoate (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA)).

Serum concentrations of OCPs, PBBs, PBDEs, and PCBs were measured using isotope dilution high resolution mass spectrometry, and isotope dilution tandem mass spectrometry for PFCs, following standard published operating procedures as previously described (Kato et al. 2011; Kuklenyik et al. 2005; Sjodin et al 2004). No automatic substitution of concentrations below the limits of detection or lipid adjustment was performed to minimize bias associated with such practices when estimating health effects (Richardson and Ciampi 2003; Schisterman et al. 2005, 2006). Serum concentrations of cotinine, quantified using liquid chromatography-isotope dilution tandem mass spectrometry (Bernert et al. 1997), and PFCs are reported in ng/mL; all other chemical concentrations are reported in ng/g serum. Serum lipids, quantified using commercially available enzymatic methods (Akins et al., 1989), were reported as total serum lipids (ng/g serum) using established methods based upon individual components including phospholipids, triglycerides, total cholesterol, and free cholesterol (Phillips et al., 1989).

*Operational definitions*. Couple fecundity was measured by TTP, which denotes the number of menstrual cycles couples required to achieve an hCG pregnancy. Couples achieving pregnancy within the first few weeks of enrollment, or before a fully observed menstrual cycle, were defined as having a TTP=0, while couples not achieving pregnancy after 12 months of trying are censored at a TTP>12. Definitions of relevant covariates included: body mass index (measured weight in kg/ height in $m^2$), gravidity (number of pregnancies), parity (number of live births), and smoking status based upon serum cotinine concentration (continous).

*Statistical analysis*. In the descriptive phase of analysis, we assessed the distributions of all exposures and relevant covariates. We analyzed data under the missing at random (MAR) assumption. Specifically, we implemented Markov Chain Monte Carlo (MCMC) methods to impute missing chemical, cotinine and lipid (≤4%) data arising from insufficient blood for analysis (Schafer, 1997). We used other chemical exposures for the imputation process. Geometric means and 95% confidence intervals (CIs) were calculated for all chemicals, cotinine and serum lipids.

We utilized daily journals supplemented with fertility monitors as needed to define menstrual cycles distinct from episodic bleeding. Specifically, a menstrual cycle denoted the interval (in days) from the onset of bleeding that increased in intensity and lasted ≥2 days to the onset of the next similar bleeding episode. Pregnancy was defined as a positive (hCG confirmed) test on the day of expected menstruation.

The analytic phase was conducted in two parts. First, we estimated unadjusted fecundability odds ratios (FORs) and accompanying 95% confidence intervals (CIs) for all 63 chemicals by class (i.e., OCPs, PBB, PBDEs, PCBs, and PFCs) using Cox models (Cox 1972) for discrete survival time (SAS version 9.2, SAS Institute, Inc., Cary, North Carolina) to estimate the odds of becoming pregnant each cycle given exposure conditional on not being pregnant in the previous cycle. This model allows the odds for pregnancy to vary from cycle to cycle through a cycle-varying intercept. Each chemical concentration (ng/g serum or wet weight) was log transformed and divided by its standard deviation to rescale concentrations to aid in the biologic interpretation of the FORs, given the small unit size for chemical concentrations. Next, for chemicals that were significantly associated with TTP based on unadjusted estimates we ran additional models adjusted for *a priori* potential confounders, i.e., continuous age, BMI, serum

cotinine, and serum lipids (except for PFC models); research site (Michigan or Texas); and the sum of the log-transformed serum concentrations of all other measured chemicals in the same class as the chemical being evaluated (ASRM 2008a; Augood et al. 1998; Hassan and Killick 2004; Ramlau-Hansen et al. 2007). In addition, we accounted for left truncation reflecting any time (≤2 months) couples were off contraception before enrollment into the study. Of note are important underlying assumptions with this approach including that months correspond to menstrual cycles, and that all unobserved time is at risk for pregnancy despite the absence of data on sexual intercourse in relation to the fertile window. Underlying linearity for all continuous covariates were assessed using Kolmogorov-type supremum test based on martingale residuals, while the proportional hazards assumptions were verified for all discrete-time models (Grambsch and Therneau, 1994; Therneau and Grambsch, 2000).

We also evaluated interactions between each chemical and age categorized as ≤27 vs. >27 for females and ≤28 vs. >28 years for males based upon previous evidence for this categorization (Dunson et al. 2002) and as corroborated in our cohort. However, we did not include interactions in our final models because none were observed.

Lastly, we ran separate models adjusted for parity in sensitivity analyses, given the uncertain causal relation between parity and persistent organochlorine pollutants (POPs) and TTP. Specifically, we modeled parity conditional on gravidity by categorizing it as: no prior pregnancy, prior pregnancy without live birth(s) and prior pregnancy with live birth(s) (Buck Louis et al. 2006).

Separate models were run for each chemical and partner. The concentrations of the chemicals evaluated were highly correlated with each other (see Supplemental Material, Figures S1 and S2 for correlations in samples from females and males, respectively) and between

partners (see Supplemental Material, Figure S3, r=0.71-0.97), which precluded joint modeling. Couples who withdrew from the study before pregnancy or before completing 12 months of follow up (n = 100) or who were not pregnant after 12 months of follow up (n = 54) were censored in all analyses. Statistical significance ($p$ <0.05) was determined using the chi-square statistic for categorical data, the Student's t-test or Wilcoxon nonparametric test for continuous data, or 95% CIs that excluded one. We did not adjust for multiple comparisons consistent with the exploratory nature of this work.

**Results**

Socio-demographic and lifestyle characteristics differed between couples that became pregnant or completed 12 months of follow up and those that withdrew before pregnancy or follow up was completed (Table 1). Participants who withdrew were more likely to self-identify as nonwhite and to be without health insurance. In comparison to women who completed the study, those who withdrew had significantly higher mean BMIs (27.2 versus 29.4 kg/m$^2$, respectively) and log-transformed serum cotinine concentrations (0.51 versus 1.08 ng/mL, respectively); the latter finding was observed for males as well (1.04 versus 1.98 ng/mL, respectively). The probability of pregnancy at cycles 1, 3, 6, and 12 were 0.27 (95% CI 0.23, 0.31), 0.52 (95% CI 0.48, 0.57), 0.68 (95% CI 0.64, 0.73), and 0.81 (95% CI 0.76, 0.85), respectively.

Table 2 presents the geometric means and 95% CIs for chemicals that were significantly associated with fecundity based upon the unadjusted FORs; for corresponding estimates for all other chemicals see Supplemental Material, Tables S1 and S2. Among the chemicals shown in Table 2, geometric means were comparable or higher in couples that withdrew before 12 months

of follow up or did not become pregnant during 12 months of follow up compared with couples who became pregnant during follow up, though only PBDE 183 and PCB 138 in men were significantly different (0.003 versus 0.002, and 0.044 versus 0.038, respectively).

Of all the chemicals tested in models adjusting for left truncation or any time off contraception prior to enrollment, only PCB 101 in men had a significant positive association with TTP (unadjusted or adjusted), indicating a shorter time to pregnancy (FOR=1.28; 95% CI 1.09, 1.51) (Table 3 and Supplemental Material, Tables S3 and S4), while all remaining significant unadjusted FORs indicated a longer TTP (Table 3). The specific chemicals that were significantly associated with reduced FORs differed between females and males, with considerably more significant negative associations noted for exposures in men. Chemicals with significant negative associations based on unadjusted models were *p,p'*-DDE, PBDE 183 and PCB congeners 101, 138, 153, 156, 157, 167, 170, 172, 180, and 209 in males, and HCB, PCB congeners 118, 167, and 209, and PFOSA in females. In adjusted models, females' serum concentrations of PCBs 118, 167 and 209 along with PFOSA were associated with an 18% to 21% reduction in fecundability per one standard deviation increase in log-transformed serum concentrations; PFOSA was associated with an 18% reduction in fecundability per standard deviation increase (FOR=0.82; 95% CI=0.71-0.95). When male serum concentrations were modeled with adjustment for covariates and left truncation, fecundability was reduced from 17% to 29% for *p,p'*-DDE and PCB congeners 138, 156, 157, 167, 170, 172, and 209.

A third important observation is the comparable reduction in fecundability for PCBs reported to be dioxin-like (#118, 156, 157, and 167) and those without dioxin-like properties, though with some differences by gender. PCB congeners 167 and 209 were consistently associated with reduced fecundability in both females (FOR = 0.79; 95% CI 0.64, 0.97 and FOR

= 0.82; 95% CI 0.68, 0.99, respectively) and males (FOR = 0.82; 95% CI 0.70, 0.96 and FOR = 0.78; 95% CI 0.65, 0.94, respectively). Adjusting for parity had little influence on model estimates (Table 3 and Supplemental Material, Tables S3 and S4).

**Discussion**

Findings from the LIFE Study, a prospective cohort of couples enrolled prior to conception and followed for up to a year while attempting to become pregnant, provide empirical evidence that selected persistent environmental chemicals from various chemical classes (i.e., OCPs, PCBs, and PFCs) may adversely affect couple fecundability. Serum concentrations among the LIFE Study participants were largely below those reported for U.S. populations during a comparable time period (CDC 2009), possibly reflecting the younger age structure of the LIFE Study cohort relative to the U.S. as a whole.

A novel finding is that the chemicals associated with reduced couple fecundability differed between males and females, but with a larger number of associations observed for males. This finding underscores the importance of males when assessing couple dependent reproductive outcomes such as TTP. However, serum concentrations of mono-ortho-PCB 167 and non-dioxin like PCB 209 were associated with approximately a 20% reduction in the probability of hCG pregnancy per standard deviation increase in the log-transformed chemical concentration in both men and women, although it is important to note serum concentrations for these PCB congeners were <LOD in 71% and 77% of women and men for PCB 167 and in 77% and 51% of women and men for PCB 209. Still, we know of no *a priori* reason or empirical evidence supporting a systematic difference in laboratory detection capability by couple

fecundability, particularly given the blinding of laboratory personnel to fecundity status in the LIFE Study. The findings warrant further inquiry, given the study's exploratory nature.

Interpreting our findings for partner-specific associations in the context of the previous literature is limited by the absence of similar preconception couple based cohorts with exposure characterization for a mixture of persistent chemicals and 12 cycles of follow up consistent with the clinical diagnosis of infertility (ASRM 2008b). Previous studies have assessed selected chemicals and TTP, but these studies were primarily among pregnant women with blood collection at varying times during gestation and retrospectively reported TTP.

Several findings from the LIFE Study are globally consistent with earlier studies that reported reduced FORs for various PCBs (Axmon et al. 2005; Buck Louis et al. 2009; Gesink Law et al. 2005), though only the results reported by Axmon et al. were statistically significant. Our findings also corroborate the lack of an association between female concentrations of *p,p'*-DDT, *o,p'*-DDT and *p,p'*-DDE and fecundability (Harley et al. 2008). Unlike Harley and colleagues' (2010) findings, we did not observe a relation between PBDEs and FORs, possibly reflecting differences in the adjusted models, or the earlier studies' use of retrospectively measured TTP. Recently, three papers have addressed the relation between select PFCs and fecundity, though only one utilized a prospective couple-based cohort design. Specifically, Vestergaard and colleagues (2012) observed no consistent pattern between eight PFCs, including PFOSA, measured in serum from 222 (52%) participating female partners who were followed for up to six cycles of attempting to become pregnant in 1992-1995. Important differences exist between this Danish Cohort and the LIFE Study, including a shorter duration of follow up (6 versus 12 cycles) in the earlier study, and choice of model specification with regard to the handling of PFCs in the context other POPs and potential confounders. When we excluded 173

(8%) cycles without intercourse during the fertile window, average TTP (4.4 cycles) changed slightly (0.4 cycle). Our PFOSA finding remained even when we limited the analysis to six cycles of follow up (FOR 0.83; 95% CI 0.70, 0.98). Two other studies of plasma PFOA and PFOS concentrations were restricted to women that had live births, and both relied upon retrospectively reported TTP, which was defined categorically (<6, 6-12, >12 months) (Fei et al. 2009) or dichotomously as subfecundity (TTP >12 months) (Whitworth et al. 2012). Fei et al. reported a significant trend between PFOA and PFOS concentrations and FORs <1 reflecting a longer TTP. Whitworth et al. reported higher odds of subfecundity, but only among parous women, a finding the authors interpreted as evidence of reverse causation, as first suggested by Olsen et al. (2009). The inclusion of parity conditional on gravidity in our sensitivity models did not substantially alter associations, which we believe is inconsistent with reverse causation. However, the association between serum PFOSA concentration in women and longer TTP, as indicated by the FOR <1, must be interpreted with caution given that concentrations were non-detectable in 90% of samples, possibly because U.S. production of PFOSA ceased in 2002.

It is important to note that the magnitude of negative associations with fecundability estimated for several of the POPs assessed in the LIFE Study are comparable to associations with other recognized fecundity determinants such as male and female age, BMI and cigarette smoking (Bolumar et al. 1996; Dunson et al. 2002; Menken et al. 1986; Ramlau-Hansen et al. 2007) that we adjusted for in our statistical models. These findings underscore the importance of environmental factors that may impact couple fecundity as measured by TTP. Our findings are relatively consistent with studies of women undergoing assisted reproductive technologies (ART) that can examine associations with early reproductive outcomes (e.g., fertilization, cleavage, implantation) that are not observable in the general population. For example, evidence

of negative associations between TTP and serum HCB and PCB 118 concentrations in women is consistent with findings for implantation failures associated with these exposures among women undergoing ART (Mahalingaiah et al. 2011; Meeker et al. 2011). While speculative, these findings suggest that associations between these chemicals and longer TTPs may reflect, in part, diminished implantation success. Still, our findings have important limitations, including the absence of information on the timing of exposures during sensitive windows for human reproduction (e.g., folliculogenesis, spermatogenesis), the absence of exposure data on short-lived chemicals such as bisphenol A and phthalates (Crain et al., 2008; Jurewicz and Hanke 2011), potential selection biases arising from enrollment of couples planning pregnancies, and possible residual confounding associated with more educated women using the monitor more effectively than lesser educated women. We did not observe any differences in frequency or timing of intercourse as aided by the monitor and female education, nor did women experience difficulties complying with the monitor (data not shown).

The etiologic mechanisms by which endocrine disrupting chemicals (EDCs), including those quantified in the LIFE Study, may affect human reproduction remain elusive, but globally are hypothesized to affect hormonal milieu through alterations in the production, release, transport, metabolism, and/or elimination of hormones (Sonnennschein and Soto 1998). With regard to ovarian function, experimental and human evidence suggests that EDCs alter both the expression/activity of enzymes required for ovarian sex steroid synthesis/catabolism, and the expression/ability of hormone receptors to bind endogenous ligands, as recently reviewed (Craig et al. 2011). Such changes occurring within the ovary are not in isolation as other endocrine organs that are relevant to reproduction, such as the thyroid, also may be affected by EDCs (Boas 2011). The potential for diverse mechanisms of action underscore the need to consider couples'

exposures in relation to a broad spectrum of human reproductive outcomes, including altered hormonal profiles or sexual libido in either partner of the couple, semen quality in the male partner (Hauser et al., 2006) and changes in menstrual and ovarian cycles (Perry et al., 2006), and effects on ovulation or implantation in the female partner. Each of these endpoints, either alone or in combination, may manifest as a longer TPP.

Delineating an underlying causal model that might explain associations between EDCs and TTP remains a critical data gap. An exposome approach that captures the totality of non-genetic exposures from conception onwards (Wild 2005) would allow chemical exposures to be evaluated in the context of lifestyle, behavior, and macro level factors that also may be relevant to human fecundity and fertility. The need for a comprehensive approach to improve understanding of risk factors and underlying mechanisms has been proposed in relation to the testicular dysgenesis syndrome (Skakkebaek et al. 2001) and, subsequently, the ovarian dysgenesis syndrome (Buck Louis et al. 2011c), both of which may result in part from early exposures that may permanently reprogram fecundity and have implications across the lifespan. Such conceptual and methodologic approaches will facilitate understanding of the up- and down-stream effects that EDCs may pose for human reproduction and health.

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**Table 1.** Comparison of study cohort by completion status, LIFE Study, 2005-2009.

| Characteristic | Completed Protocol (n=401) | Withdrew (n=100) |
|---|---|---|
| | Mean ± SD or N (%) | Mean ± SD or N (%) |
| Female characteristics | | |
| Age | 29.9 ± 3.9 | 30.4 ± 4.9 |
| Gravidity | 1.0 ± 1.2 | 1.3 ± 1.5 |
| Parity | 0.6 ± 0.8 | 0.7 ± 1.0 |
| Body mass index (kg/m$^2$)** | 27.2 ± 7.1 | 29.4 ± 7.8 |
| Serum lipids (ng/g) | 617.1 ± 115.1 | 642.3 ± 157.2 |
| Serum cotinine (ng/mL)[a#] | 0.51 ± 1.40 | 1.08 ± 1.19 |
| Nonwhite[#] | 74 (19) | 34 (34) |
| High school graduate/GED or less | 21 (5) | 10 (10) |
| No health insurance[#] | 20 (5) | 20 (20) |
| | | |
| Male characteristics | | |
| Age | 31.7 ± 4.7 | 32.1 ± 5.8 |
| Body mass index (kg/m$^2$) | 29.8 ± 5.5 | 29.7 ± 5.8 |
| Serum lipids (ng/g) | 728.9 ± 214.1 | 741.5 ± 220.9 |
| Serum cotinine (ng/mL)[a##] | 1.04 ± 2.02 | 1.98 ± 2.54 |
| Nonwhite[#] | 73 (18) | 34 (34) |
| High school graduate/GED or less[#] | 26 (7) | 23 (23) |
| No health insurance* | 28 (7) | 14 (14) |

*$p < 0.05$; **$p < 0.01$; [#]$p < 0.001$; [##]$p=0.0001$

[a]Cotinine was log-transformed

SD, standard deviation

**Table 2.** Geometric mean values of persistent environmental chemical concentrations by observed pregnancy status during follow-up, LIFE Study, 2005-2009.

| Chemical (ng/g serum) | LOD | % <LOD | Became pregnant (n=347) Geometric mean (95% CI) | Withdrew or not pregnant during follow up (n=154)[a] Geometric mean (95% CI) |
|---|---|---|---|---|
| Female exposures | | | | |
| HCB | 0.013 | <1 | 0.046 (0.045-0.048) | 0.048 (0.044-0.051) |
| PCB 118[b] | 0.0026 | <1 | 0.017 (0.016-0.018) | 0.018 (0.016-0.020) |
| PCB 167[b] | 0.0026 | 75 | 0.003 (0.003-0.003) | 0.004 (0.003-0.004) |
| PCB 209 | 0.0026 | 77 | 0.002 (0.002-0.002) | 0.002 (0.002-0.002) |
| PFOSA (ng/mL) | 0.1 | 90 | 0.110 (0.100-0.122) | 0.126 (0.106-0.151) |
| Male exposures | | | | |
| *p,p'*-DDE | 0.013 | <1 | 0.766 (0.721-0.814) | 0.818 (0.737-0.908) |
| PBDE 183 | 0.0026 | 67 | 0.002 (0.002-0.002)** | 0.003 (0.002-0.003) |
| PCB 101 | 0.0026 | 62 | 0.003 (0.003-0.003) | 0.003 (0.002-0.003) |
| PCB 138 | 0.0026 | <1 | 0.038 (0.036-0.041)* | 0.044 (0.039-0.049) |
| PCB 153 | 0.0026 | <1 | 0.057 (0.053-0.061) | 0.063 (0.057-0.071) |
| PCB 156[b] | 0.0026 | 7 | 0.007 (0.007-0.008) | 0.008 (0.007-0.009) |
| PCB 157[b] | 0.0026 | 71 | 0.002 (0.002-0.003) | 0.003 (0.002-0.003) |
| PCB 167[b] | 0.0026 | 71 | 0.003 (0.003-0.003) | 0.004 (0.003-0.004) |
| PCB 170 | 0.0026 | 1 | 0.017 (0.016-0.018) | 0.019 (0.017-0.021) |
| PCB 172 | 0.0026 | 62 | 0.003 (0.003-0.003) | 0.003 (0.003-0.004) |
| PCB 180 | 0.0026 | <1 | 0.044 (0.041-0.048) | 0.049 (0.043-0.054) |
| PCB 209 | 0.0026 | 51 | 0.003 (0.003-0.003) | 0.003 (0.003-0.003) |

NOTE: Chemicals with a significant unadjusted fecundability odds ratio only. For geometric mean values of all other chemicals see Supplemental Material, Tables S1 and S2.

[a]Includes women who either withdrew from study at varying stages of trying and who did not become pregnant.

[b]Dioxin-like compounds.

*p < 0.05; **p < 0.01

LOD, limit of detection of the analytical method

**Table 3.** Environmental chemicals[a] by partner and fecundability odds ratios (FOR), LIFE Study, 2005-2009.

| Chemical[b] | Unadjusted FOR (95% CI) | Adjusted[c] FOR (95% CI) | Adjusted[d] FOR (95% CI) | Sensitivity Model[e] FOR (95% CI) |
|---|---|---|---|---|
| Female Model | | | | |
| HCB | 0.87 (0.77, 1.00)* | 0.95 (0.81, 1.11) | 0.94 (0.80, 1.10) | 0.96 (0.82, 1.13) |
| PCB 118[f] | 0.87 (0.77, 0.99) | 0.88 (0.75, 1.02) | 0.82 (0.68, 0.98) | 0.84 (0.70, 1.01) |
| PCB 167[f] | 0.88 (0.78, 0.99) | 0.87 (0.76, 1.00) | 0.79 (0.64, 0.97) | 0.81 (0.66, 1.00)* |
| PCB 209 | 0.87 (0.75, 1.00)* | 0.86 (0.72, 1.02) | 0.82 (0.68, 0.99) | 0.77 (0.62, 0.95) |
| PFOSA (ng/mL) | 0.82 (0.72, 0.93) | 0.81 (0.70, 0.94) | 0.82 (0.71, 0.95) | 0.82 (0.71, 0.95) |
| | | | | |
| Male Model | | | | |
| *p,p'*-DDE | 0.88 (0.78, 0.99) | 0.83 (0.70, 0.97) | 0.83 (0.70, 0.97) | 0.80 (0.67, 0.94) |
| PBDE 183 | 0.83 (0.71, 0.96) | 0.86 (0.73, 1.01) | 0.86 (0.73, 1.01) | 0.85 (0.72, 1.00)* |
| PCB 101 | 1.18 (1.03, 1.36) | 1.27 (1.08, 1.49) | 1.28 (1.09, 1.51) | 1.24 (1.05, 1.46) |
| PCB 138 | 0.84 (0.74, 0.97) | 0.83 (0.70, 0.99) | 0.71 (0.52, 0.98) | 0.69 (0.50, 0.94) |
| PCB 153 | 0.86 (0.75, 0.98) | 0.86 (0.73, 1.02) | 0.67 (0.42, 1.06) | 0.68 (0.43, 1.06) |
| PCB 156[f] | 0.85 (0.75, 0.96) | 0.84 (0.71, 0.99) | 0.77 (0.62, 0.96) | 0.76 (0.61, 0.94) |
| PCB 157[f] | 0.86 (0.77, 0.97) | 0.87 (0.75, 1.00) | 0.83 (0.70, 0.97) | 0.82 (0.70, 0.96) |

**Table 3.** Environmental chemicals[a] by partner and fecundability odds ratios, LIFE Study, 2005-2009 – cont.

| Chemical[b] (ng/g serum) | Unadjusted FOR (95% CI) | Adjusted[c] FOR (95% CI) | Adjusted[d] FOR (95% CI) | Sensitivity Model[e] FOR (95% CI) |
|---|---|---|---|---|
| PCB 167[f] | 0.86 (0.75, 0.98) | 0.85 (0.73, 0.99) | 0.82 (0.70, 0.96) | 0.82 (0.70, 0.96) |
| PCB 170 | 0.85 (0.75, 0.96) | 0.84 (0.71, 1.00)[*] | 0.74 (0.56, 0.98) | 0.75 (0.58, 0.96) |
| PCB 172 | 0.87 (0.77, 0.99) | 0.88 (0.75, 1.04) | 0.82 (0.68, 0.99) | 0.81 (0.67, 0.98) |
| PCB 180 | 0.87 (0.76, 0.98) | 0.88 (0.74, 1.04) | 0.81 (0.66, 1.00) | 0.81 (0.66, 0.98) |
| PCB 209 | 0.84 (0.73,0.96) | 0.83 (0.70,0.97) | 0.78 (0.65,0.94) | 0.78 (0.65, 0.93) |

[a]Restricted to chemicals with a significant association with fecundability based on unadjusted models. See Supplemental Material, Tables S3 and S4 for corresponding estimates for all other chemicals evaluated.

[b]Serum concentrations were log transformed then rescaled by their standard deviations to enhance the interpretation of effect sizes.

[c]Adjusted for the sum of all other chemicals in the same chemical class, age (categorized), BMI (continuous), log-transformed serum cotinine (continuous), log-transformed serum lipids (continuous) except in PFC models, and site (Michigan or Texas).

[d]Adjusted for left truncation to account for time off contraception before enrollment and sum of all other chemicals in the class of compounds, age (categorized), BMI (continuous), cotinine (continuous), lipids (continuous) except in PFC models, and site (Michigan/Texas).

[e]Sensitivity analysis adjusting for parity conditional on gravidity, in addition to left truncation and the other covariates listed above.

[f]Dioxin-like compounds.

[*]CI significant before rounding to two decimal places (≤0.998).